VALUE IN HEALTH 18 (2015) 1043–1049

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/jval

Quality of Life and Asthma Symptom Control: Room for Improvement in Care and Measurement

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ABSTRACT

Background: The recent Global Initiative for Asthma management strategy recommends achieving symptom control and minimizing the future risk of poor outcomes as priorities for asthma management. **Objective:** The objective was to quantify the association between symptom control and health-related quality of life in asthma. **Methods:** In a prospectively recruited random sample of adults with asthma, we ascertained symptom control and measured health-related quality of life using a generic (EuroQol five-dimensional questionnaire [EQ-5D]) and a disease-specific (Asthma Quality of Life Questionnaire) instrument, to estimate EQ-5D and five-dimensional Asthma Quality of Life Questionnaire (AQL-5D) utilities, respectively. We measured the adjusted difference in utilities across symptom control levels and calculated the loss of predictive efficiency due to aggregating multiple symptoms into one symptom control variable. **Results:** The final sample included 958 observations from 494 individuals (mean age at baseline 52.2 ± 14.5 years; 67.0% women). Asthma was symptomatically controlled, partially controlled, and uncontrolled in 269 (28.1%), 367 (38.3%), and 322 (33.6%) observations, respectively. A person with symptomatically uncontrolled asthma would gain 0.0512 (95% CI 0.0339–0.0686) in EQ-5D or 0.0802 (95% CI 0.0693–0.0910) in AQL-5D utilities by achieving symptom control. The loss of predictive efficiency was 55.4% and 27.6% for EQ-5D and AQL-5D utilities, respectively. **Conclusions:** Asthma symptom control status corresponds well with both generic and disease-specific quality-of-life measures. The trade-off, however, between ease of use and predictive power should be reconsidered in developing simplified measures of control. Our results have direct relevance in informing decision-analytic models of asthma and deducing the effect of interventions on quality of life through their impact on asthma control.

Keywords: asthma, observational studies, quality of life, regression analysis.

Introduction

Impairment due to asthma can have a substantial impact on quality of life [1]. Because there are no realistic options to completely prevent or cure asthma, the emphasis of current asthma management guidelines is to control the manifestations of the disease [2,3]. One of the most widely used measures of asthma control is the definition developed by the Global Initiative for Asthma (GINA). In the most recent version of the GINA management strategy, assessment of asthma control is divided into assessing *symptom control* and risk factors for future poor asthma outcomes [4]. This is a departure from the previous GINA strategy, which included both symptoms and lung function metrics in the definition of *clinical* control [5].

Given the central role of asthma control as a framework for the management of asthma, guidelines have emphasized the use of asthma control as a relevant outcome both in clinical practice and in research [3]. From a policy perspective, however,

Conflict of interest: M. Sadatsafavi has received research funding paid directly to the University of British Columbia from the Canadian Institutes of Health Research and AstraZeneca Canada. J. M. FitzGerald has served on advisory boards for GlaxoSmithKline, AstraZeneca, Novartis, Pfizer, Boehringer-Ingelheim, Takeda, and Merck. He has also been a member of speakers' bureaus for GlaxoSmithKline, AstraZeneca, Novartis, Aerocrine, Boehringer-Ingelheim, Pfizer, and Merck. He has received research funding paid directly to the University of British Columbia from the Canadian Institutes of Health Research, AstraZeneca, GlaxoSmithKline, Boehringer-Ingelheim, and Merck. He is a member of the Global Initiative for Asthma (GINA) and is chair of the GINA Executive and a member of its Science Committee. The rest of the authors have indicated that they have no conflicts of interest with regard to the content of this article.

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1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2015.07.008

measuring the merits of asthma interventions will require mapping the causal relationships between asthma control and policy-relevant outcomes such as costs and quality of life. Estimating the impact of interventions on health-state utility values (utilities) enables quantification of their health impact in terms of quality-adjusted life-year (QALY) as the metric of choice for cost-effectiveness studies [6]. As such, estimates of change in utility as a result of change in asthma control can be of value in informing decision-analytic models of asthma.

Developing simple and easy-to-use measures of asthma control involves aggregating different metrics to calculate one or more global scores. In the case of GINA symptom control, the four domains with binary (yes/no) responses create 16 permutations, which are then reduced to a three-level symptom control variable. Such an aggregation inevitably results in loss of information. Evaluating the impact of information loss in terms of the efficiency of the GINA definition of symptom control in predicting policy-relevant outcomes will help researchers refine such measures. In the present study, we investigated such issues using the 2014 GINA definition of asthma symptom control as it relates to quality of life. The primary objective of this study was to quantify the gain in quality of life that can be achieved by achieving GINA symptom control in patients with symptomatically uncontrolled or partially controlled asthma. We pursued several secondary objectives: to estimate the loss of predictive efficiency by aggregating four symptom domains into a single symptom control variable, to evaluate the relative influence of individual symptom domains on quality of life, and to evaluate the impact of the removal of lung function measurement in the recent GINA definition on its association with quality of life.

Methods

Study Population

This study was based on data from the Economic Burden of Asthma, a prospective observational study aimed at measuring the economic and humanistic burden of asthma at the population level (University of British Columbia Human Ethics no. H10-01542). Details about the study have been described elsewhere [7,8]. Through random digit dialing in two census areas in British Columbia, Canada, the study recruited 618 individuals with self-reported, physician-diagnosed asthma. The census areas consisted of the Metro Vancouver and Okanagan regions (2011 populations of 603,502 and 179,830, respectively [9]); these areas were chosen to represent both urban and rural populations. Eligibility criteria also included having had at least one asthma-related encounter with the health care system in the past 5 years, not being pregnant or planning to become pregnant in the next 12 months, and planning to reside in the study area for the next 12 months. The follow-up time was 12 months, with visits scheduled every 3 months. At baseline and final visits, individuals underwent spirometry and responded to an asthma symptoms questionnaire, permitting the evaluation of asthma control according to both 2012 and 2014 GINA guidelines [2]. The final visit was generally around 1 year after entry; however, for participants who notified the investigators of their withdrawal, spirometry was performed in their last visit before withdrawal. The subsample for the present study included adults in whom both asthma control and quality of life had been measured at first and/or last visits.

Exposure

The main exposure was symptom control as defined by the 2014 GINA management strategy [4]. This definition is based on four domains, which focus on outcomes from the past 4 weeks, each taking a binary value (no = 0, yes = 1): daily symptoms (two or less vs. more), limitations of activities (none vs. any), nocturnal symptoms/awakening (none vs. any), and need for reliever or rescue treatment (two or fewer vs. more). The previous (2012) GINA management strategy defined clinical control (as opposed to symptom control) on the basis of the same symptom domains plus a fifth domain that is the ratio of forced expiratory volume in 1 second (FEV_1) to its predicted value (cutoff 80%) [5]. For the sake of brevity, we use the term *control* to refer to clinical control or symptom control, respectively, whenever the 2012 or 2014 versions of GINA management strategies are considered. In both versions, asthma is defined as uncontrolled if three or more of the domain values are positive, partially controlled if one or two values are positive, and controlled otherwise.

Outcomes

Individuals at baseline and all follow-up visits filled out a generic preference-based instrument (EuroQol five-dimensional questionnaire [EQ-5D], three-level version [10]), as well as the short version of the Asthma-related Quality of Life Questionnaire (mini-AQLQ [11]). We used the National Health and Nutrition Examination Survey reference standards for estimating predicted FEV_1 values [12]. Both EQ-5D and AQLQ responses were converted to health-state utility values (utilities). To derive EQ-5D utilities, we used the algorithm as described by Dolan et al. [13]. For AQLQ, we followed the two-step approach as described by Yang et al. [14]: first, the response levels were reduced from seven to five as proposed in Young et al. [15] and then the algorithm proposed by Yang et al. [14] was used to calculate five-dimensional Asthma Quality of Life Questionnaire (AQL-5D) utilities. Given that the latter weight is based on a UK sample, we also used UK tariffs for the EQ-5D to ensure comparability [13].

Statistical Analysis

All statistical analyses were performed in SAS (version 9.3, Carey, NC). Two-tailed *P* values at the 0.05 level were evaluated for statistical significance. The unit of observation in this study was a study visit resulting in concomitant assessment of both utilities and asthma control. Chi-square test for categorical variables and analysis of variance for continuous variables were used to examine the distribution of variables across control levels.

Adjusted analyses were based on fitting regression models that would associate utilities with asthma control, adjusting for potential confounding variables. Given that a proportion of individuals would report a utility value of 1, the assumptions of normally distributed regression residuals, required for inference in the conventional ordinary least squares (OLS) regression, would not be satisfied. We therefore used a two-part regression model, with logistic and OLS components [16]. The logistic component was fitted to model the impact of independent variables on the probability of having a utility of 1, and an OLS regression was fitted in the subset of individuals with a utility of less than 1 to model the linear effect of independent variables on utility values. We used generalized linear models with generalized estimating equations for both components to account for the clustering of observations (visits) within individuals [17]. The three-level GINA control variable entered the model as two dummy variables representing partially controlled and uncontrolled asthma with the reference being controlled asthma. Inference was made using parametric bootstrapping with 100 replications. For both components, we chose the following covariates as potential confounders: age at baseline visit, sex, income (high vs. low at the cutoff of Can $60,000 per year), education level (high [postsecondary education or higher] vs. low),

place of birth (Canada vs. elsewhere), residence type (rural vs. urban), and insurance coverage for medications (complete vs. partial vs. no coverage).

Primary Objective—the Relationship between Symptom Control and Quality of Life

The adjusted "marginal" effect of symptom control on utilities was recovered by combining regression coefficients from the logistic and OLS parts using G-computation [16,18]. G-computation operates by calculating the predicted values from both regression components, thus enabling the calculation of the expected utility under a given exposure level (uncontrolled, partially controlled, or controlled asthma) for each individual in the sample. Marginal values are recovered by averaging the predicted utilities within each level of control across the sample [18]. Provided that there are no unmeasured confounders, the marginal estimates can be interpreted causally as the expected change in utility by achieving control for a random subject with uncontrolled (or partially controlled) asthma.

We performed additional sensitivity analyses. We repeated the analysis by restricting the data to first visit as well as to the last visit. In addition, the subsample of individuals who had different asthma control status in at least two visits provides an alternative opportunity of estimating change in utility. We fitted a separate two-part model for this subsample with change in utility as the dependent variable and change in asthma control as the independent variable to estimate the effect of change in asthma control on utilities from this "within-individual" design [19].

Secondary Objectives

Predictive Efficiency of GINA Definition of Symptom Control

We investigated the predictive power (for predicting utilities) lost by aggregating the four symptom domains into a single symptom control variable. This was performed by comparing the coefficient of determination (R^2), the ratio of variance of utility explained by the model over the total variance [20], for three two-part models for utilities (separately for the EQ-5D and the AQL-5D). Model 1 included only covariates, model 2 included covariates and GINA symptom control, and model 3 included covariates plus four symptom domains and their first-order interaction terms. We defined the loss of efficiency as follows:

$$\text{Loss of efficiency} = (R^2 \text{ of model 3} - R^2 \text{ of model 2}) / (R^2 \text{ of model 3} - R^2 \text{ of model 1})$$

The numerator is the gain in R^2 that would have been achieved by using full range of symptom domains compared with using the GINA symptom control, and the denominator is the maximum possible gain in R^2; thus, the ratio will be between 0 and 1 and can be presented in percentage.

Relationship between Symptom Domains and Utilities

We created a reference two-part model with covariates and symptom domains and their first-order interaction as predictors (similar to model 3). From this model, we estimated the reduction in R^2 when a particular symptom domain is removed from the model. The most influential symptom domain is the one whose removal results in the largest drop in R^2.

Results

A total of 496 adults contributing 961 observations with asthma were eligible for this study. Three study visits were excluded because symptoms or lung function were not properly recorded. The final sample consisted of 958 observations from 494 unique individuals. Mean age at baseline was 52.2 ± 14.5 years; women comprised 67.0% of the sample. Table 1 presents the baseline characteristics of observations in total as well as within symptom control levels. Recruitment occurred between January 2011 and July 2012. The average time between the first and final visits was 375.1 days (range 185–485; 5th–95th percentile 349–426).

Table 1 – Demographic characteristics of the sample across study visits, according to the level of control*.

Variable	All n = 9	Controlled n = 69	Partially controlled n = 367	Uncontrolled n = 22	*P*
Age (y), mean ± SD	52.36 ± 14.47	53.04 ± 15.01	51.41 ± 14.64	52.89 ± 13.78	<0.01*
Sex (%)					<0.01*
Male	32.9	40.5	34.3	24.8	
Female	67.1	59.5	65.7	75.2	
Income (%)					0.01*
Low	57.1	47.2	42.0	53.4	
High (>60K/y)	42.9	52.8	58.0	46.6	
Education (%)					0.20
Low	24.5	28.3	22.1	24.2	
High	75.5	71.7	77.9	75.8	
Place of birth (%)					
Canada	70.8	70.3	71.7	70.2	0.89
Foreign born	29.2	29.7	28.3	29.8	
Residence type (%)					<0.01*
Urban	91.0	92.2	93.7	87.0	
Rural	9.0	7.8	6.3	13.0	
Insurance for medications (%)					0.17
None	15.4	19.3	14.2	13.7	
Partial	63.2	58.7	65.1	64.6	
Complete	19.2	17.1	18.5	21.7	

* The unit of observation is study visits.

Table 2 – Utility scores across and within visits.

Visit	Mean ± SD (n)				P
	All	Controlled	Partially controlled	Uncontrolled	
EQ-5D					
Both visits	0.916 ± 0.129 (n = 958)	0.945 ± 0.097 (n = 269)	0.922 ± 0.127 (n = 367)	0.884 ± 0.146 (n = 322)	<0.001*
First visit	0.908 ± 0.125) (n = 494)	0.936 ± 0.095 (n = 127)	0.916 ± 0.121 (n = 194)	0.878 ± 0.141 (n = 173)	<0.001*
Last visit	0.924 ± 0.133 (n = 464)	0.952 ± 0.098 (n = 142)	0.928 ± 0.133 (n = 173)	0.891 ± 0.153 (n = 149)	<0.001*
Difference	0.015 ± 0.006	0.019 ± 0.008	0.009 ± 0.011	0.014 ± 0.013	<0.001*,†
AQL-5D‡					
Both visits	0.927 ± 0.077	0.969 ± 0.045	0.935 ± 0.065	0.884 ± 0.088	<0.001*
First visit	0.924 ± 0.081	0.970 ± 0.047	0.934 ± 0.068	0.880 ± 0.091	<0.001*
Last visit	0.930 ± 0.073	0.968 ± 0.043	0.935 ± 0.063	0.889 ± 0.084	<0.001*
Difference	0.006 ± 0.003	–0.001 ± 0.004	–0.002 ± 0.006	0.008 ± 0.008	<0.001*,†

* Significant at the 0.05 level.
† Represents the statistical significance of change between first and last visits in utilities across control groups.
‡ Numbers of observations are similar to the corresponding values in the top half of the table.

In general, our study sample comprised mostly those with mild asthma, represented by a low rate of asthma-related emergency department visits (10.7%) or hospitalizations (4.0%) in the year before enrollment. In 269 (28.1%), 367 (38.3%), and 322 (33.6%) visits, asthma was symptomatically controlled, partially controlled, or uncontrolled, respectively. The distribution of several baseline variables was significantly different across control levels (Table 1).

Table 2 presents the unadjusted comparison of utility scores across symptom control groups, separately within the first and last visits, as well as for both visits combined. In all comparisons, the difference in both EQ-5D and AQL-5D utility scores across control levels was statistically significant, with a gradient of decreasing mean utility values with less controlled asthma. Across all visits, 531 (55.4%) of EQ-5D and 189 (19.7%) of AQL-5D values were 1. Distribution of EQ-5D and AQL-5D domains across symptom control levels is provided in Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2015.07.008.

Primary Outcome

Table 3 provides results of the two-part regression model relating symptom control to EQ-5D and AQL-5D utility scores. There was a significant reduction for symptomatically uncontrolled compared with symptomatically controlled asthma in both EQ-5D (difference –0.0512; 95% confidence interval [CI] –0.0686 to –0.0339) and AQL-5D (difference –0.0802; 95% CI –0.0910 to –0.0693) utilities. Similarly, for partially controlled asthma, there was a significant reduction for both EQ-5D (difference –0.0217; 95% CI –0.0344 to –0.0089) and AQL-5D (difference –0.0337; 95% CI –0.0430 to –0.0243) utilities. Regression coefficients for independent variables are provided in Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2015.07.008.

Results of sensitivity analyses are provided in Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2015.07.008. Limiting the observations to only the first visit or the final visit did not substantially change the results. However, the difference in utilities across control levels was smaller in the within-individual analysis. The change in utilities from uncontrolled to controlled asthma was 0.0285 for the EQ-5D utility ($P = 0.10$) and 0.0278 for the AQ-5D utility ($P < 0.01$). The corresponding values for change from partially controlled to controlled asthma were 0.0023 ($P = 0.88$) and 0.0199 ($P = 0.02$), respectively.

Secondary Objectives

Predictive Efficiency of GINA Definition of Symptom Control

The regression model that included only covariates could explain 8.8% and 10.3% of the variation in the EQ-5D and the AQL-5D, respectively. The addition of GINA control variable increased this to 11.5% and 27.3%, respectively. The model with individual symptom domains, however, increased the explained variation to 14.9% for EQ-5D and 33.8% for AQL-5D utilities. As such, the loss of

Table 3 – Change in utility by change in level of control: Effect (95% confidence interval).

Variable	EQ-5D	AQL-5D
Partially controlled (vs. controlled)		
Adjusted odds ratio for reporting perfect utility	0.69 (0.49–0.97) $P = 0.032$*	0.27 (0.18–0.39) $P < 0.001$*
Adjusted utility loss for those who reported imperfect utility	–0.0214 (–0.0495 to 0.0067) $P = 0.135$	–0.0273 (–0.0370 to –0.0175) $P < 0.001$*
Adjusted loss of utility	–0.0217 (–0.0344 to –0.0089) $P < 0.01$*	–0.0337 (–0.0430 to –0.0243) $P < 0.01$*
Uncontrolled (vs. controlled)		
Adjusted odds ratio for reporting perfect utility	0.48 (0.33–0.70) $P < 0.001$*	0.12 (0.07–0.20) $P < 0.001$*
Adjusted utility loss for those who reported imperfect utility	–0.0445 (–0.0755 to –0.0136) $P = 0.135$	–0.0705 (–0.0838 to –0.0573) $P < 0.001$*
Adjusted loss of utility	–0.0512 (–0.0686 to –0.0339) $P < 0.01$*	–0.0802 (–0.0910 to –0.0693) $P < 0.01$*

* Significant at the 0.05 level.

Table 4 – Variance components (R^2).

Independent variables*	EQ-5D (%)	AQL-5D (%)
Covariates only	8.8	10.3
Covariates + GINA 2014 (symptom) control variable	11.5	27.3
Covariates + individual symptom domains	14.9	33.8
Efficiency loss	55.4	27.6
Proportion of variance explained when GINA 2014 domain variables are removed		
Covariates + individual symptom domains except *daily symptoms*	14.8	33.1
Covariates + individual symptom domains except *limited activities*	11.1	24.6
Covariates + individual symptom domains except *nocturnal symptoms*	13.7	31.0
Covariates + individual symptom domains except *need for reliever*	14.8	33.3
Proportion of variance explained with 2012 GINA definition of clinical control		
Covariates + GINA 2012 (clinical) control variable	11.1	27.2

AQL-5D, five-dimensional Asthma Quality of Life Questionnaire; EQ-5D, EuroQol five-dimensional questionnaire; GINA, Global Initiative for Asthma.

* All numbers are R^2 from the two-part model (ratio of explained variance to total variance), with the exception of efficiency loss, whose definition is provided in the text.

predictive efficiency of GINA symptom control definition was 55.4% for EQ-5D and 27.6% for AQL-5D utilities (Table 4, top section).

Relationship between GINA Symptom Domains and Quality of Life

The middle section of Table 4 demonstrates the influence of individual symptom domains on explaining the variation in EQ-5D and AQL-5D utilities. For both, the domain with the largest influence was limited activities. The influences of three other domains on explaining the variance of utilities were lower but were similar with each other.

The Impact of removing FEV_1 from the Definition of Asthma Control

When the 2012 GINA definition of asthma control was applied to the study sample, in 183 (19.1%), 400 (41.8%), and 375 (39.1%) observations, asthma was categorized as being controlled, partially controlled, and uncontrolled, respectively. Compared with the 2014 GINA symptom control definition, the use of 2012 GINA asthma control variable reduced the R^2 from 11.5% to 11.1% for EQ-5D and from 27.3% to 27.2% for AQL-5D utilities (Table 4, bottom section).

Discussion

We performed a detailed analysis of the association between symptom control levels as defined in 2014 GINA management strategy with quality of life in a random sample of patients with asthma. We estimated that by achieving symptom control in a patient with symptomatically uncontrolled asthma, a gain of 0.0512 in EQ-5D and 0.0802 in AQL-5D utilities could be achieved. Assuming that we have adequately adjusted for confounding variables, the reported change in utilities across control levels can directly be used in decision-analytic models of asthma that use GINA-defined asthma control as their core disease states. We also showed that aggregating individual symptom domains into a single symptom control variable is associated with substantial loss of predictive power especially when EQ-5D utilities are concerned. Among the four symptom domains, limitation in activities was mostly correlated with quality of life. Finally, we showed that as long as quality of life is concerned, relocating lung function metrics from symptom control to risk factors for worse outcomes in the latest GINA recommendations seems justifiable.

In the sensitivity analysis that estimated the difference between utilities from within-individual observation pairs, estimates were smaller, and for EQ-5D utilities they were not statistically significant. This can be interpreted as this analysis being more robust than the main analysis in controlling for unmeasured time-fixed confounders. Within-individual studies, however, are subject to other threats to validity such as carry-over, recall, and demand (prevarication) biases [21]. First, the sample that experienced different levels of control between the first and last visits does not constitute a random sample of the target population. In addition, in this particular context, individuals' assessment of asthma control and utility values can be affected by their recall of previous responses, resulting in dilution of regression coefficients. Also, GINA asthma control is an aggregate measure and individuals could still vary within a given level. Therefore, the magnitude of within-individual changes in symptom control between the two visits might have been more limited than the difference between two independent visits. A *post hoc* analysis of the data indicated the presence of such phenomena. The average number of present symptoms was 3.17 (out of 4) in instances of uncontrolled asthma that had a paired controlled asthma status, whereas this value was 3.53 for all other instances of uncontrolled asthma. Overall, we believe that given both exposure and outcomes are subjectively assessed, within-individual designs might be susceptible to bias, and our main analysis that uses all observations based on a model for the full data is a more robust approach, provided that it has sufficiently accounted for confounding factors.

To our knowledge, this is the first study of the association between asthma symptom controls, as defined by the latest GINA management strategy, and utilities. Previous studies have reported on the association between various measures of asthma control and quality of life [1,22–30], but for the most part the authors did not use utilities for quality of life; thus, quantification of the outcome in terms of QALYs was not possible. Also, many studies simply reported average utility scores across control levels. Although informative, these unadjusted results can be confounded by factors that affect quality of life and asthma control, and thus cannot be causally interpreted. Two exceptions are the studies by Chen et al. [1] and Briggs et al. [29]. In the former study, after adjusting for several potential confounding variables, asthma control as defined by the Asthma Therapy Assessment Questionnaire [31] had a clear dose-response association with EQ-5D utilities. In Briggs et al. [29], the association between asthma control levels, as defined similarly to previous GINA definitions, and AQLQ-derived utilities was evaluated using the data of a large randomized trial [29]. Randomization on treatment does not protect against the confounding effect of factors affecting asthma control and quality of life, and the regression model was not adjusted for important confounders such as sex or socioeconomic status, but the association was controlled for asthma severity in terms of the intensity of treatment in the run-in period [29].

The fact the GINA control and its domains were more strongly associated with AQL-5D scores as disease-specific utilities is not a surprise given that they are both based on asthma-related impairment. However, the fact that limitation in activities is the strongest predictor is worthy of consideration. Both exposure and outcome assessment instruments (GINA symptom control, EQ-5D, and AQLQ) have items concerning activity limitations, and this might have resulted in strong correlations around activity limitation. The magnitude of explanatory power attributed to each component of asthma control is, in part, a function of characteristics of the instrument selected as the dependent variable, and not necessarily reflective of the underlying construct. Utilities estimated using more robust methods such as standard gamble or time trade-off can provide better insights in this regard.

Currently, all variables are given the same weight as daytime and nocturnal symptoms and need for relievers, but a definition that assigns more weight to variables that are more strongly associated with quality of life can potentially improve the correlation of symptom control with quality of life and reduce the loss of predictive power. Whether such a gain in efficiency is acceptable at the cost of increased complexity requires further considerations. However, it can be argued that a robust measure of control should correlate well with not only quality of life but also resource use and costs. Nevertheless, with the separation of the risk of future adverse outcomes, which most likely determine costs, from symptom control in the recent GINA definition, we argue that the association of symptom control with quality of life is the most relevant metric for its performance, thus justifying attempts to improve the predictive power of symptom control with respect to quality of life.

The limitations of our study should be considered. First, scoring functions for both the EQ-5D and the AQL-5D are derived on the basis of responses from the UK population; as a result, they may differ from the preferences of the Canadian population. Our EQ-5D scores and associated utility values were higher than those of the normative values (UK population) [32] as well as the recently reported Canadian values [33], despite the fact that individuals in our study sample had asthma to begin with. A likely reason for this phenomenon is the healthy volunteer bias associated with a clinical study in which participants had to attend the study sites multiple times. Given the likely broader range of the distribution of quality of life in the general asthma population and the higher level of morbidity, our results might be an underestimate of the effect of asthma control on quality of life (i.e., the gain in quality of life with improving asthma control would likely be larger in the general population than in our study sample). Another limitation is that, due to overlap in some of the questions between GINA, the EQ-5D, and the AQL-5D, recall bias might have played a role in creating a positive correlation. Direct elicitation of utilities using standard gamble or time trade-off can overcome this potential bias. In addition, our study was restricted to the four symptom domains included in the definition of GINA symptom control. There might be other symptom domains or variables whose inclusion in the assessment of asthma control can further enhance its association with quality of life. This remains to be studied in the future.

We particularly designed our study such that results can inform decision-analytic models of asthma that predict longitudinal transition across control levels. We did not adopt a longitudinal design (associating baseline control and follow-up utilities) because the interest was in the magnitude of association between current control level and utility. This is required for decision-analytic models of asthma that assign utility values to asthma control states. The longitudinal design, although more robust in drawing causal estimates between control and utility, would underestimate the quantity of interest because of the contamination of exposure groups (due to within-individual changes in control over time) as described in Hernan et al. [34]. Another important consideration in this regard is that none of our study participants at any of the study visits reported experiencing an exacerbation of asthma. As such, the estimated gain in utilities from this analysis does not include the gain associated with a lower rate of exacerbations when asthma is better controlled. We do not see this as a drawback of our study. Decision-analytic models of asthma often explicitly incorporate exacerbations and associated reduction in quality of life [29]; thus, the utility values across control levels should exclude the effect of exacerbations as well in order to be informative to such models.

In many jurisdictions, the prevalence of poorly controlled asthma is high [35]. However, the conventional wisdom is that with proper management, asthma control can be achieved in most of the patients [36]. Given that inexpensive and effective treatments are available for this purpose, uncontrolled asthma represents a gap in care and a preventable source of burden. We specifically showed that efforts in achieving symptom control can be associated with significant gain in quality of life. In addition, our study points out toward potentials for improvement in the assessment tools for asthma control. Designing measurement tools that can correlate well with policy-relevant outcomes can enhance our abilities to provide efficient care and design and implement efficient interventions for the management of asthma.

Acknowledgments

We thank members of the Economic Burden of Asthma study team for their valuable help: Roxanne Rousseau, Douglas Rolf, Satvir Dhoot, Lisa Dinh, Jennie Chan, Jesmin Dhillon, Gurleen Gill, Jessika Iwanski, Zaakir Jiwa, Intan Agoes, Richie Li, Jordan Deppiesse, Samantha Gray, Elena Terekhova, Nicole Brunton, Dayna Taylor, Madeline Ludwig, Laura FitzGerald, Douglass Rolfe, and Wan Tan Hogg.

Source of financial support: This study has been funded through the Collaborative Innovative Research Fund, an investigator-initiated, peer-reviewed competition sponsored by GlaxoSmithKline Canada. None of the sponsors played a role in the study design, data analysis, interpretation, or publication of the results. The sponsor did not review the manuscript before submission. The authors express no apparent or perceived conflict of interest.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2015.07.008 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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